Screening and prevention of diabetic blindness

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ABSTRACT. Diabetic eye disease remains a major cause of blindness in the world. Laser treatment for proliferative diabetic retinopathy and diabetic macular edema became available more than two decades ago. The outcome of treatment depends on the timing of laser treatment. The laser treatment is optimally delivered when high-risk characteristics have developed in proliferative retinopathy or diabetic macular edema and before this has significantly affected vision. Laser treatment is usually successful if applied during this optimal period whereas the treatment benefit falls sharply if the treatment is applied too late. In order to optimize the timing of laser treatment in diabetic eye disease screening programs have been established. The oldest screening program is 20 years old and several programs have been established during the last decade. In this paper the organisation and methods of screening programs are described including direct and photographic screening. The incidence and prevalence of blindness is much lower in populations where screening for diabetic eye disease has been established compared to diabetic populations without screening. Technical advantages may allow increased efficiency and telescreening.

From a public health standpoint screening for diabetic eye disease is one of the most cost effective health procedures available. Diabetic eye disease can be prevented using existing technology and the cost involved is many times less than the cost of diabetic blindness.

Key words: diabetes mellitus – diabetic retinopathy – blindness – preventive medicine – screening – laser treatment – telemedicine – public health – medical economics.

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Diabetic eye disease, in particular diabetic retinopathy, is one of the most common causes of blindness in the western world. It remains a major cause of blindness in spite of the fact that diabetic blindness can to a large degree be prevented with existing technology through a public health approach utilizing systematic screening and preventive treatment. In this paper we will review the scientific foundations on which a public health approach to diabetic blindness is based. We will discuss different approaches to screening for diabetic eye disease, including direct screening by ophthalmologists, photographic screening, telescreening and technical developments relating to screening procedures. We will review the outcome studies from diabetic blindness prevention programs and compare this to the incidence and prevalence of diabetic blindness in other populations. Finally, the socio-economic impact of diabetic blindness and its prevention will be discussed.

General diabetes management

The diabetes control and complications trial demonstrates that the general management of diabetic patients, in particular the control of blood glucose levels, is important in reducing the progress of diabetic retinopathy (Diabetes Control and Complications Trial reports 1987, 1993, 1995, 1996). Careful control of arterial hypertension, abstinence from smoking and careful management of the diabetic during pregnancy is also important. The favourable effect of glycaemic control and blood pressure control has also been confirmed in type 2 diabetics (UK Prospective Diabetes Study 1998). Prevention of diabetic blindness rests upon a co-operation between the internist or general practitioner who manages the disease and the ophthalmologist who will intervene once the eye disease has reached a sight threatening stage.

Laser treatment

Retinal photocoagulation has been a recognised treatment for diabetic retinopathy for decades and twenty years ago the diabetic retinopathy study showed conclusively that panretinal photocoagulation is a very effective way of reducing the risk of blindness in proliferative retinopathy (Diabetic Retinopathy Study Research Group, 1976, 1981). Similarly, the Early Treatment Diabetic Retinopathy Study verified that macular laser treatment is effective in reducing the risk of blindness in diabetic macular edema, the other major cause of blindness in diabetic retinopathy (ETDRS Research Group 1985).

The vast majority of blindness in diabetics results from either proliferative

diabetic retinopathy or diabetic macular edema and this is still true today, even though effective treatment for both these conditions has been known for at least 15–20 years. So why are diabetics still going blind? One reason is that the timing of laser treatment is very important. Diabetic retinopathy tends to progress with time. The optimal time for treating diabetic macular edema is when it has reached clinically significant state (ETDRS 1985) and preferably before visual acuity is significantly affected. This means that the optimal time period for treating the patients with diabetic macular edema is in a time period when the patient does not yet have significant visual symptoms. Similarly, the optimal time period for laser treatment for proliferative diabetic retinopathy is when preretinal vessels have developed and before a significant vitreous haemorrhage or traction retinal detachment has developed. Again, the optimal time period for treatment is before the patient develops visual symptoms. Laser treatment for diabetic retinopathy is a preventive treatment which is ideally given to the asymptomatic patient. The only way to assure that the patients are treated in this optimal time period is through regular screening of diabetics so that the need for treatment can be assessed through fundus examination. In the absence of screening, treatment will be applied only after the patient has developed visual symptoms, in which case the treatment is usually more difficult and the outcome worse.

Criteria for screening

Cuckle & Wald (1984) have defined seven criteria that a disease entity must fulfill to be considered suitable for screening:

1. The disorder should be well defined.
2. Estimates of its prevalence and rate of progression should be available.
3. There should be an effective treatment.
4. The screening test should be simple and safe and capable of discriminating adequately between affected and unaffected patients.
5. Those with a positive test should have a sufficiently high probability of being affected.
6. The facilities for a screening program should be available or easily installed.
7. The program should be cost effective.

Diabetic eye disease fulfills Cuckle's criteria for screening. The disorder is well defined and classification systems exists such as the Early Treatment Diabetic Retinopathy Study classification (ETDRS 1991) The prevalence and rate of progression has been studied in a number of epidemiologic studies (Klein et al. 1984, 1989, 1992; Agardh et al. 1993, 1996; Kristinsson et al. 1994, 1997). Laser treatment for proliferative diabetic retinopathy and diabetic macular edema has been shown to be a very effective treatment which reduces the rate of visual loss in diabetic patients with proliferative retinopathy and macular edema by at least 50% (ETDRS 1985 and Diabetic Retinopathy Study 1981). Screening for diabetic retinopathy is easily done by an ophthalmologist through a standard eye examination with slitlamp biomicroscopy of the fundus with the aid of a 60, 78 or 90 diopter lens or alternatively through fundus photography where the fundus

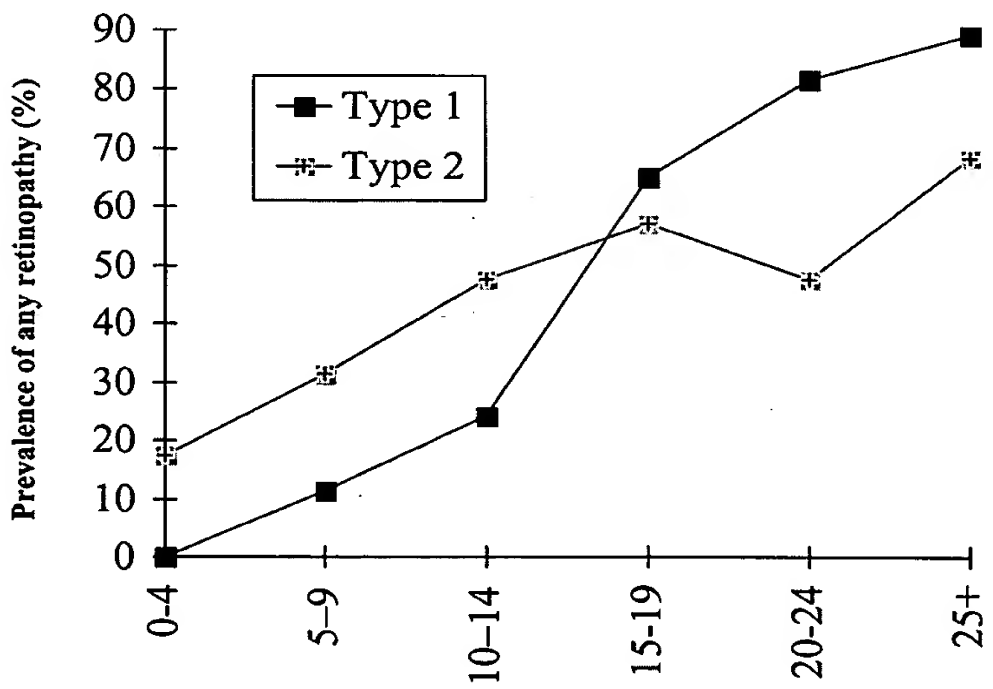

Fig. 1. This figure shows the prevalence of any retinopathy in type 1 diabetics (dark boxes) and type 2 diabetics (light boxes). The data is based on a cross sectional population study in Iceland (Kristinsson et al. 1997).

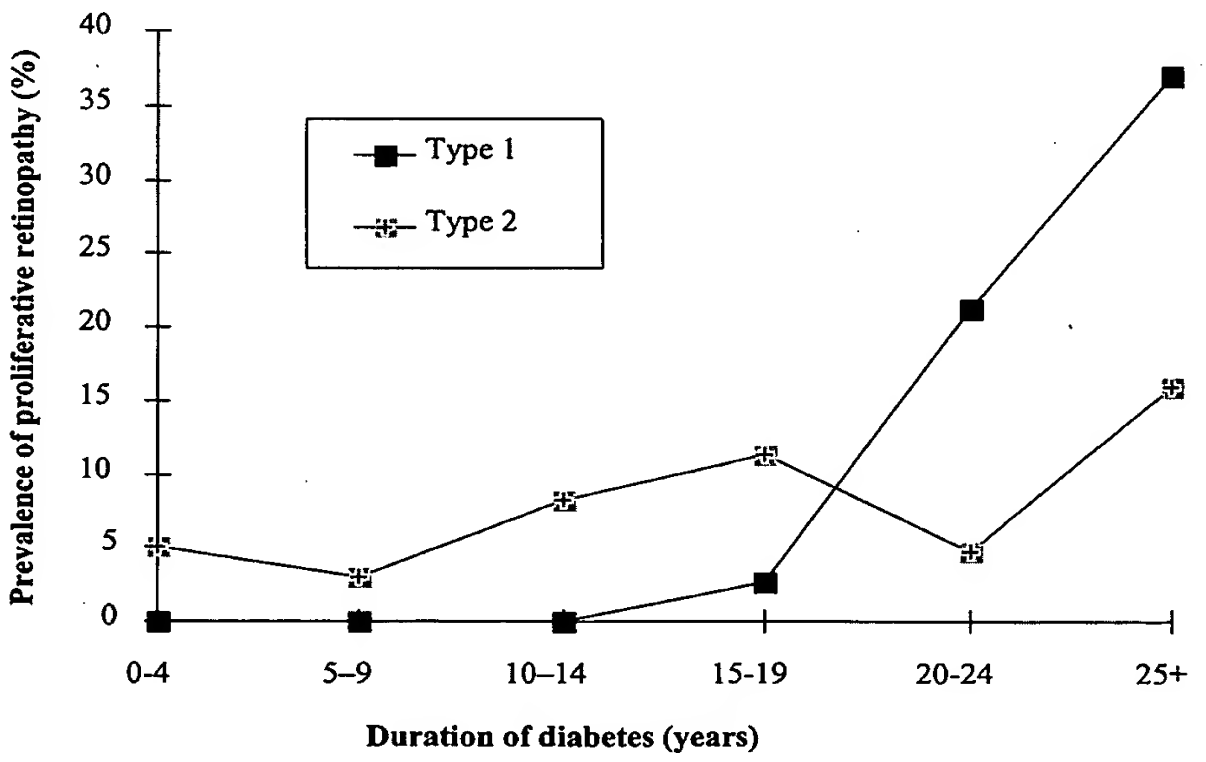

Fig. 2. This figure shows the prevalence of proliferative retinopathy in type 1 diabetics (black boxes) and type 2 (light boxes). The data is based on a cross sectional population study in Iceland (Kristinsson et al. 1997).

photographs are then graded by a trained grader or an ophthalmologist. Such a screening examination has a high degree of specificity and sensitivity for diabetic retinopathy (Moss et al. 1985; Kalm et al. 1989 & 1993; Harding et al. 1995). Facilities for a screening program involve equipment found in most eye clinics, including a slitlamp and a fundus camera.

Javitt et al. (1990, 1991, 1994, 1995, 1996) has tested the economic feasibility of diabetic screening. He tested 5 different screening models including dilated ophthalmoscopic examination every two years, every year or every six months with or without fundus photography. All forms of screening were found to be highly economical and cost-saving for the government.

Epidemiology of Diabetic Retinopathy

The prevalence of diabetic retinopathy is related to the duration of diabetes. The prevalence is usually low in the first years after diagnosis and after more than 20 years of type 1 diabetes mellitus most diabetics have some retinopathy (Fig. 1) and 30–40% have proliferative diabetic retinopathy (Fig. 2).

The increasing prevalence of diabetic retinopathy with duration of diabetes is also seen with type 2 diabetes mellitus in which retinopathy is sometimes seen at the time of diagnosis (Fig. 2). The average prevalence of retinopathy in type 2 diabetes is in most studies between 30 and 40% (Fig. 1) with up to 10% having macular edema and a similar proportion with proliferative retinopathy (Figs. 2, 3).

The average prevalence, however, can be misleading if the duration of diabetes is not taken into account. In the Icelandic type 1 diabetic population the prevalence of any retinopathy goes from zero at the time of diagnosis to almost 90% after 20 years of diabetes (Fig. 1) and at the same time the prevalence of proliferative disease goes from zero to about 35% (Fig. 2) and macular edema from zero to about 25% (Fig. 3). Henricsson et al. (1996) have reported similar duration related prevalence in Swedish diabetics. A relationship between retinopathy and duration of diabetes is seen in both insulin dependent and non-insulin dependent diabetes (Figs 1, 2, 3). In general, the majority of diabetics can be expected to develop retinopathy with time and 30–50% can be expected to develop sight-threatening retinopathy, namely proliferative retinopathy or diabetic macular edema, in their lifetime. This is the proportion of diabetics that can expect to benefit from the timely laser treatment resulting from regular screening.

Incidence of retinopathy

In type 1 diabetics Kristinsson et al. (1997) found the four-year incidence of any retinopathy to be 38%, with a 6.6% four-year incidence of proliferative retinopathy and 3.4% four-year incidence of macula edema. Klein et al. (1989) reported a somewhat higher incidence in Wisconsin, namely 59% four-year incidence for any retinopathy, 10.5% for proliferative disease and 8.2% with macular edema (Fig. 4). The difference between these populations may be due to a difference in average blood sugar levels, which are higher in the diabetics in Wisconsin.

In diabetics with age at onset over 30 years Klein et al. (1989) found the four-year incidence of any retinopathy to be 47%, and 7% for proliferative retinopathy in those using insulin, but a lower four-

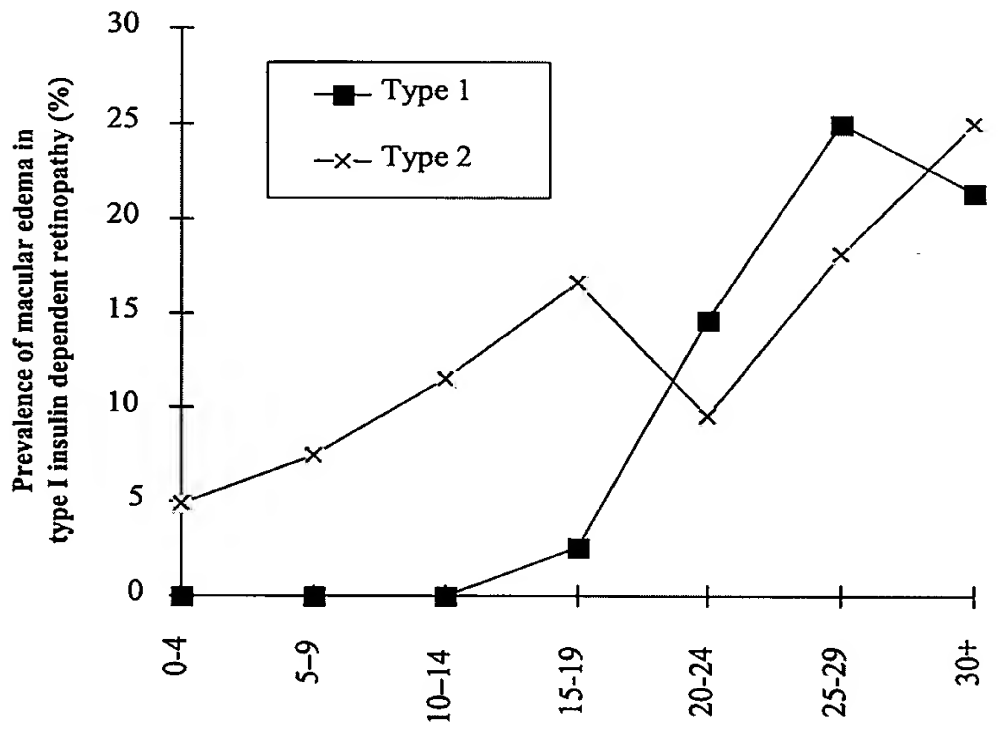

Fig. 3. This figure shows the prevalence of diabetic macular edema in type 1 diabetics (black boxes) and type 2 diabetics (light boxes). The data is based on a cross sectional population study in Iceland (Kristinsson 1997).

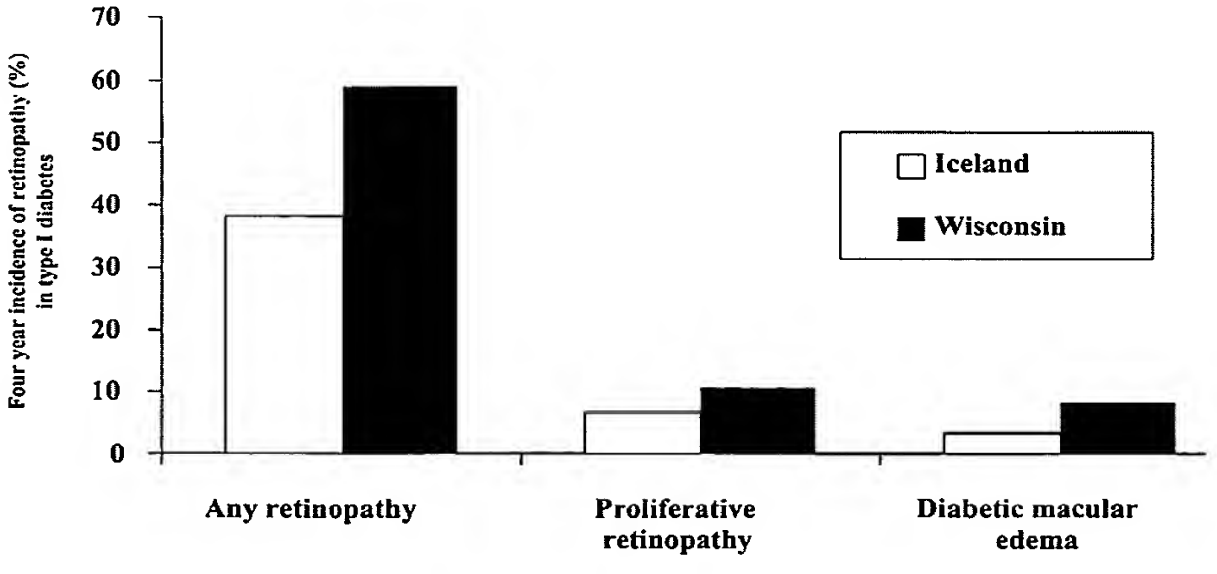

Fig. 4. This graph shows the reported incidence over 4 years of progressing from no retinopathy to any retinopathy; progressing to proliferative retinopathy; and progressing to diabetic macular edema. The data for Iceland is shown in white columns (Kristinsson et al. 1997) and data for Wisconsin is shown in black columns (Klein et al. 1989).

year incidence of 34% and 2%, respectively, for those who do not use insulin.

Visual Impairment in Diabetics

Prevalence of blindness

Diabetes mellitus is a major cause of blindness in the world. Kahn and Hiller (1974) estimated that diabetes accounted for 10% of all new cases of blindness and 20% of new cases of blindness in patients 45–74 years of age. In the United Kingdom Sorsby (1972) found that diabetic retinopathy was the single leading cause of new blindness in England and Wales in patients between ages 30 and 64, accounting for 15% of all new registered blindness. 10 years later Ghafour et al. (1983) found that diabetic retinopathy was the most common cause of blindness in the age-group of 45–64 years in the west of Scotland, accounting for 10% of registered blindness, and at the same time Doesschate (1982) found diabetes to be the leading cause of blindness in the Netherlands, accounting for 21% of reported blindness.

Sjølie and Green (1987) found the prevalence of blindness in a Danish population to be 5.9% in diabetics with a duration of more than 8 years and estimated the prevalence of blindness in diabetics to be 50–80 times higher than in the normal population.

A considerable difference in the prevalence of diabetic blindness is seen when comparing diabetic populations that have been involved in systematic screening programs with those who have not. In type 1 diabetics involved in a screening program in Iceland the prevalence of legal blindness was found to be 1% and the prevalence of partial sight 2.5% (visual acuity <0.1 and <0.3 respectively) (Kristinsson et al. 1994). In diabetic populations not involved in screening programs Nielsen (1982) found a prevalence of legal blindness of 5.7% in a Danish population. Jerneld and Algvere (1987) reported prevalence of legal blindness of 7.7% and 9.3% with partial sight in a Swedish population. Klein et al. (1984) reported a 3.6% prevalence of legal blindness and 4.6% partial sight in the United States (Fig. 5).

In Iceland a systematic screening program for diabetic eye disease was started around 1980. At that time the prevalence of legal blindness in the diabetic population was 2.4% and in 1994 this had decreased to 0.5%, demonstrating a substantial benefit of the screening program (Fig. 6) (Kristinsson 1997).

Incidence of blindness

The incidence of visual impairment is high in diabetic populations not involved in active screening and much lower in populations that receive active screening and prevention. Nielsen (1984) studied a diabetic population in Denmark not involved in active screening and reported a 1-year incidence of legal blindness of 3.7% in type 1 diabetics (receiving insulin) and 1.9% in type 2 diabetics treated with diet and/or oral agents. In the same group the incidence of visual impairment (visual acuity between 0.1 and 0.3) was 3.7% for the type 1 and 2.2% for the type 2 diabetics. It must be taken into account that these figures include reduced vision from causes other than diabetes, such as age related macular degeneration, cataracts and retinal vein occlusions. In another Danish population Sjølie and Green (1987) reported a 1% annual incidence of blindness and in a diabetic population in Wisconsin, Moss et al. (1988) reported a 1.5% four-year incidence of blindness corresponding to about 0.4% annual incidence.

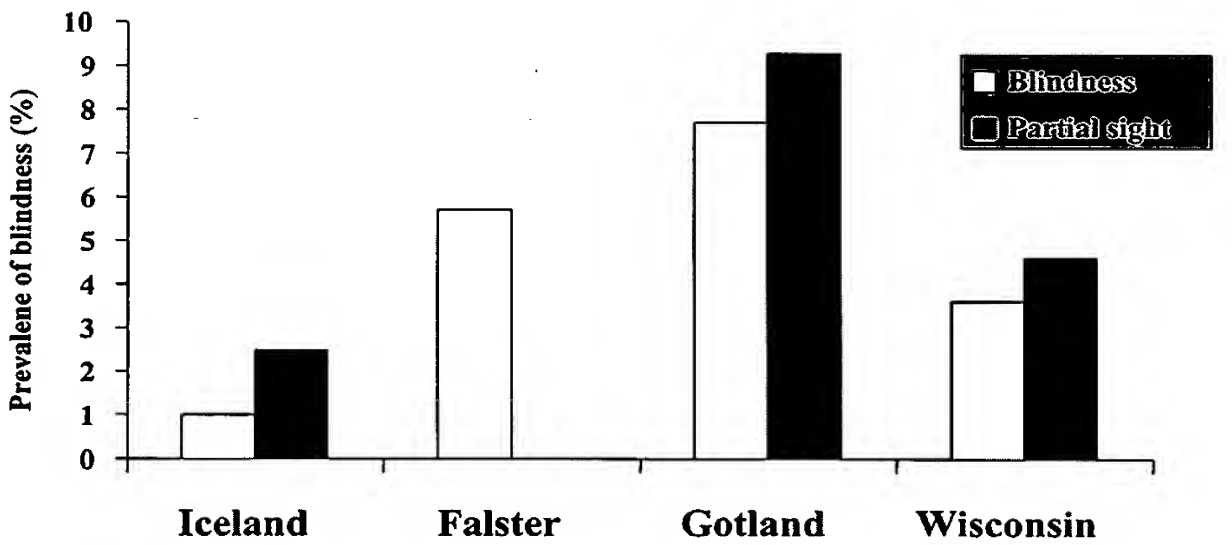

Fig. 5. Prevalence of blindness and partial sight in type 1 diabetics. Legal blindness (visual aquity less than 0.1) and is shown with white columns and partial sight (visual aquity less than 0.3) is shown with black columns. Prevalence data is shown from the diabetic population in Iceland where a screening program had been in place for more than 10 years (Kristinsson et al. 1994) and in three populations of insulin dependent diabetics where no screening program was in place, namely in Falster in Denmark (Nielsen 1982), Gotland in Sweden (Jerneld and Algvere 1987) and Wisconsin (Klein et al. 1984).

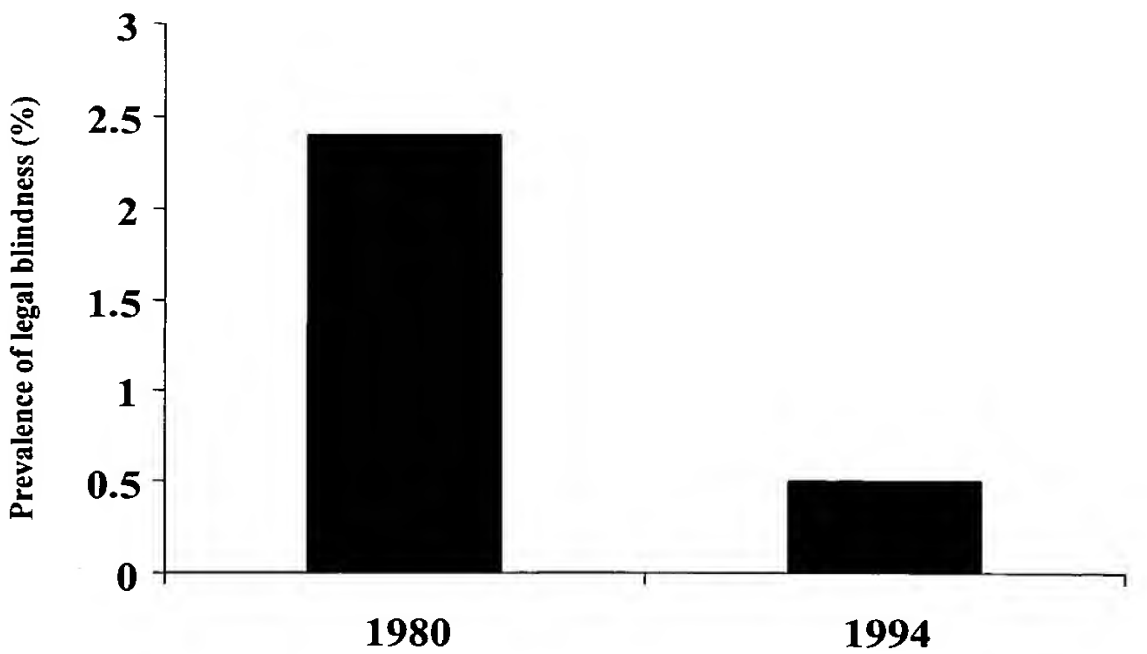

Fig. 6. Prevalence of legal blindness in insulin dependent diabetics in Iceland in 1980 at the beginning of the screening program and again in 1994. The difference is statistically significant (p=0.02) (Kristinsson et al. 1997).

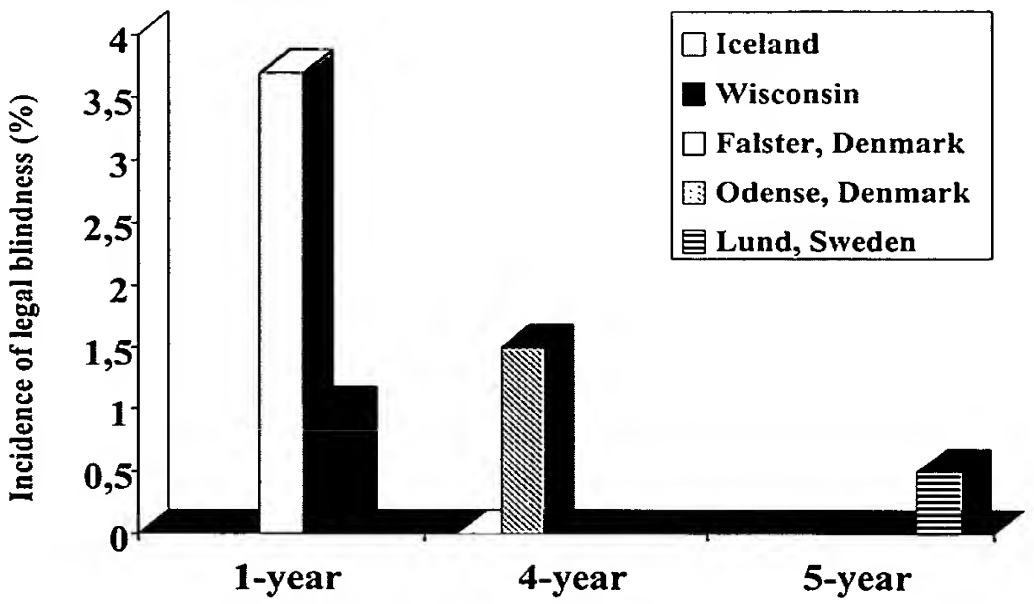

Fig. 7. Incidence of legal blindness in insulin dependent diabetics. The figure shows the one year incidence of legal blindness in Falster, Denmark (Nielsen 1984) and Odense Denmark (Sjølie 1987) in two diabetic populations that were not involved in a screening program. The four year incidence of legal blindness is shown in type 1 diabetics in Iceland who had been involved in a screening program from more than 10 years (Kristinsson 1994a) and in type 1 diabetics in Wisconsin (Moss et al. 1988). Finally, the five year incidence of legal blindness in a Swedish population of type 1 diabetics involved in a screening program is shown (Agardh 1993). The populations involved in screening programs have a low incidence of legal blindness (0.0–0.1% yearly incidence), whereas the populations not involved in screening have yearly incidence of legal blindness of 0.4–3.7%.

These numbers are in stark contrast to the incidence found in diabetic populations involved in active screening. Agardh et al. (1993) reported a five-year incidence of legal blindness of 0.5% in a diabetic population involved in active screening. This corresponds to about 0.1% annual incidence. Kristinsson et al. (1994) reported a zero incidence of legal blindness in 175 type 1 diabetics involved in a rigorous screening program in Iceland (Fig. 7). Similar findings were reported by Henricsson et al. (1996) who studied a diabetic population involved in a regular photographic screening program. The yearly incidence of legal blindness was zero in 404 diabetics with onset under age 30 and 0.13% in 1729 diabetics with onset over age 30. The respective incidence of visual impairment was 0.34% and 0.50%.

Evolution of visual results

Once efficient methods for treatment of diabetic retinopathy were established in the early eighties and clinical guidelines not only for how but also for when treatment is most beneficial were available, screening programs for early detection of sight-threatening diabetic retinopathy became important. By regular screening and proper treatment it was felt that the incidence of blindness could be decreased by 1/3 or more in European countries (St. Vincent Declaration 1989; Kohner & Porta 1992).

Since the eighties, treatment of both the metabolic conditions of diabetes and diabetic retinopathy have improved, and it is difficult to estimate to what extent screening programs are responsible for reduced blindness and visual impairment and what role is played by better metabolic and blood pressure control. It has been suggested, however, that screening and early treatment of diabetic retinopathy would prevent deterioration of visual acuity and could reduce the risk of blindness due to diabetic retinopathy by 56% (Rohan et al. 1989). Therefore, it was disappointing to learn that in north-west Italy, the incidence of retinopathy-related blindness did not show any trend to decrease between 1967 and 1991 (Porta et al. 1995).

Several studies have been published where screening programs for early detection of sight-threatening diabetic retinopathy are associated with low incidence figures for blindness and visual impairment in type 1 diabetic patients (Agardh et al. 1993; Henriksson et al. 1996; Kristinsson et al. 1997) where the three- to five-year incidence rates of blindness were 0%-0.5%. These rates are considerably lower than those reported in the 14-year follow-up Wisconsin study of 1998, where screening was not generally available (Moss et al. 1998). The Wisconsin figures in turn, are lower than those of Sjölie and Green 1987, probably reflecting some lack of photocoagulation treatment options during the eighties. For comparison, an extrapolation of the results is shown in Table 1. Thus regular retinal examinations, timely detection, and treatment of vision-threatening diabetic retinopathy (Agardh et al. 1993; Henriksson et al. 1996; Kristinsson et al. 1997) leads to low blindness rates in type 1 diabetic patients.

Despite regular screening examinations, prevention of visual impairment is not as successful in type 2 as in type 1 diabetes (Agardh et al. 1993), mostly due to progressing macular edema. Since visual acuity loss in these patients is usually irreversible, it is of utmost importance to recognize clinically significant macular edema and refer those patients for laser treatment early in the course of retinopathy. Delay of photocoagulation treatment due to late referral was found to result in an increased number of legally blind eyes (Agardh et al. 1996).

Methods for Screening

Screening for diabetic eye disease is usually performed with either direct screening by ophthalmologists or photographic screening. Direct screening is performed by an ophthalmologist in a standard eye clinic applying slitlamp exami-

Table 1. Cumulative incidence of blindness in type 1 diabetic populations calculated to a 14-year period.

	Screening	Photocoagulation	Blindness
Sjölie and Green 1987	–	?	11.6%
Wisconsin 1998	–	(+)	2.4%
Agardh et al. 1993	+	+	1.4%
Henricsson et al. 1996	+	+	0%
Kristinsson et al. 1997	+	+	0%

nation of the fundus using 60, 78 or 90 diopter lens. Photographic screening involves a photographer taking fundus photographs through dilated pupils and the figures are graded by an ophthalmologist at a later time. Both techniques have been used in a number of centers and good success has been achieved with either technique.

Direct screening

In a direct screening program the diabetic will be called in by the clinical co-ordinator for eye examination at regular intervals. The diabetic will undergo a standard eye examination including measurement of visual acuity, applanation tonometry in patients over 40 for glaucoma screening, slitlamp examination and examination of the fundus through dilated pupils with slitlamp biomicroscopy and a 60, 78 or 90 diopter lens. The screening ophthalmologist will determine the stage of retinopathy and inform the patient at once. He will also determine the need for further studies or treatment which can be scheduled or carried out at the same time. Fundus photography is performed for documentation with a standard fundus camera.

Since this type of eye screening is usually performed at an eye clinic it is vital to keep a close link with the diabetes clinics, endocrinologists and general practitioners. This involves sending regular reports of screening examination and treatment to the physicians involved in the diabetes care. It is also essential to educate the diabetics on diabetic retinopathy and explain to them the rationale behind the screening program.

Direct screening programs can be established using existing eye clinics and do not require any equipment not usually available in a standard ophthalmology practice. The key to the success of a direct screening program is a clinic co-ordinator who maintains a register of the diabetic patients involved in the program, calls them in for screening visits at the appropriate time intervals and maintains the clinical data and photographic archives necessary. The screening effort is supported by a medical retina clinic where fluorescent angiographies and argon laser treatment is carried out as indicated by the Diabetic Retinopathy Study Research Group and ETDRS Research Group criteria.

Photographic screening

One of the five targets in the St. Vincent declaration (1989) was to reduce blindness due to diabetes with one-third or more over five years. Therefore a workshop was held in 1990 at Hammersmith Hospital, London, in order to define a protocol for the screening for diabetic retinopathy in Europe (Screening for Diabetic Retinopathy in Europe: A field guidebook). Recommendation was given on how to organise retinopathy screening. Standard photos of different stages of diabetic retinopathy were published in the booklet in order to establish agreement on what to refer for laser treatment.

The timing of laser treatment for diabetic retinopathy is very important. However, due to the symptomatic silence of diabetic retinopathy the patient may be unaware of sight threatening retinopathy that is in need of laser treatment. Therefore screening procedures are required. Photographic screening of the diabetic retina has shown good sensitivity and specificity in detecting retinal lesions in diabetes and this type of screening calls for a simple and systematic organisation.

Organisation and patient record

As photographic screening calls for a simple and systematic organisation, ophthalmic photography clinics should be close to or integrated in the environment where the routine diabetes check is performed and they can be set up in the diabetes out-patient clinics or in mobile vans driving round the community. Standard information about the general health of the patient should be included in the eye-record and should be edited and updated at every visit. The standard data are easily managed on paper files, but can also be placed in an electronic patient database and should include:

1) Patient ID
2) Type and onset of diabetes
3) Systemic complication due to diabetes (neuropathy (amputation), nephropathy (micro/macro proteinuria, dialysis, transplantation), hypertension (medical treatment), cardiac disease (by-pass surgery, pacemaker, smoking habits))
4) Body-mass index
5) Record of previous eye disease or treatment (amblyopia, glaucoma, cataract, laser (periphery, macula), vitrectomy (silicone oil installation, retinal detachment)
6) Metabolic regulation (HbA1c)
7) Arterial blood pressure
8) Visual acuity unaided and with glasses and/or pinhole
9) Date for the last retinal examination
10) Information of diabetic treatment (diet, oral agents or insulin)
11) Information of any pharmacological treatment

Photographic Fundus Examination

Retinal photographs are useful in the screening for diabetic retinopathy because the photographs

1. Are stored in patient records as documentation for any progression of the disease
2. Make a basis for quick evaluation of patients and decision for further assessment or treatment
3. Allow the physician to reassure patients and advise on next attendance
4. Give information to the internists or general practitioners.

Dilation of the pupils

Retinal photography can be done in either mydriatic or non-mydriatic cameras, but pharmacological mydriasis is recommended even in non-mydriatic cameras. The pupils should be dilated with 1% tropicamide and/or 2.5% phenylephrine eye drops in order to achieve the best quality of fundus photos with no shadows from the edge of the pupil.

Camera and fields of the retina

Depending on the type and the angle of width of the camera different methods for photographing the retina are recommended. Cameras are available in 30–60° angles and on some cameras the angle can be adjusted. Some of the cameras can be used in non-mydriatic situations, but for screening purposes they should be used only with dilated pupils. For screening purposes at least two fields of the retina should be photographed using a 45° or 50°-60° angle camera. One picture should be centered at the macula and the second picture should be centered at the optic disc. Using a 7 field non-stereoscopic 30° photography (Arlie House) inferior and superior parts of the peripheral retina should be included. Stereoscopic photography of certain parts of the retina can be included especially of the macula region in order to assess macular oedema. In general, 7 field stereoscopic (ETDRS Research Group) photography of the retina is not used for daily clinical screening, but reserved for scientific purposes.

Film

Photographs should be obtained on 35 mm colour slides or red-free transparencies. Instant prints are not recommended because of their lesser resolution and poorer conservation over time. The 35 mm colour have been shown to be more sensitive in detection of cotton wool spots and hard exudates as well as IRMA (intra retinal microvascular abnormalities) and proliferation. Monochrome photographs are on the other hand more sensitive to microaneurysms and dot-blot hemorrhages in the retina. So far, the gold standard for fundus photos is the 35 mm transparent colour film, however, digital photography is likely to replace film in the coming years.

Assessments

One of the main advantages of using photographic technique for fundus screening is the ability to compare the photograph with standard photos. Furthermore, this technique allows the grader to compare the current pictures with previous pictures from the same patient, easily enabling a quick overview of the status of the retina. When they are available, the grader is able to determine the degree of macular oedema from stereoscopic fundus photos. Well-trained graders can screen fundus photos from 20–30 patients per hour.

In order to standardise photo assessment and the communication with the internist, it is recommended that a standard grading scheme is used where the status of the retina is described in the following fixed sentences, to which information on stability, regression and progression can be added:

1. No retinopathy
2. Mild/Moderate/Severe background retinopathy
3. Pre-proliferative retinopathy
4. Proliferative retinopathy
5. Significant/non-significant macular oedema.

Screening Intervals

As a rule, diabetic retinopathy is not seen before puberty in children and therefore regular eye screening of young diabetic children is not indicated. The American Academy of Ophthalmology has suggested that regular screening should start at age 10 years and the American Diabetes Association suggest that screening should start at age 12 in those who have had diabetes for at least 5 years (Singer 1992). European guidelines have similarly suggested that regular screening is unnecessary before age 10 and should be started at puberty (Retinopathy Working Party). In Iceland diabetic retinopathy is as a rule not seen in children under age 12 and regular screening is thus not started before this age (Kristinsson et al. 1995). It is easier to use an age limit rather than the onset of puberty which can vary between individuals.

The American College of Physicians, American Diabetes Association and the American Academy of Ophthalmology have recommended that all type 1 diabetic patients be examined annually. They also recommend that type 2 diabetic patients be examined at the diagnosis of diabetes, four years later if no retinopathy is detected and annually after that (Singer 1992). The Retinopathy Working Party (1991) has suggested a screening protocol for diabetic retinopathy in Europe advising that all diabetic patients should be examined at diagnosis, at least every other year thereafter and at least annually if retinopathy appears, and more frequently as needed. This seems very appropriate, as diabetic retinopathy will usually not progress from no retinopathy to sight threatening retinopathy in less than two years (Kristinsson et al. 1995) which makes biannual screening for diabetics without retinopathy appropriate, whereas the four-year interval at the beginning of the process in type 2 diabetics as recommended by the American Academy of Ophthalmology, risks the onset of sight threatening retinopathy during that period. In Sweden, the National Board of Health and Welfare have included regular screening for retinopathy every other year for all diabetic patients in the national guidelines for diabetes.

Kalm (1993) recommends screening intervals in a photographic screening program that takes into account duration of diabetes. With no retinopathy or only background retinopathy she recommends five-year intervals in patients with five-year duration of diabetes, followed by three, two and one-year intervals with a duration of diabetes of 10, 15 and 20 years, respectively. For type 2 diabetic patients Kalm recommends three-year intervals for those with no retinopathy.

Javitt et al. (1990) examined five different strategies in the screening using a computer model. They compared screening every six months, every year and every two years and came to the conclusion that examining patients with no retinopathy every year and those with retinopathy every six months gave the best cost benefit. Similarly, Dasbach et al. (1991), using a computer model to calculate cost effectiveness, concluded that annual screening was more effective than similar screening every other year. It must be taken to account that these are theoretical calculations. The Icelandic screening system has been very successful in applying biannual screening for those without retinopathy, annual screening for patients with background retinopathy and more frequent screening as deemed appropriate for those with more severe retinopathy (Kristinsson et al. 1995).

Telescreening in Diabetic Retinopathy

Background

Tele is Greek, meaning "far away". Telescreening in diabetic retinopathy means that the assessment of screening data consisting of a fundus photograph and some clinical background information is made far from where the patient is examined. There are several reasons why telescreening is relevant in the context of screening for diabetic retinopathy, such as lack of ophthalmologists that can assess retinopathy, especially in geographically remote areas (Bek et al. 1998).

During the recent years major advances in information technology have provided the technological basis for implementing telescreening for diabetic retinopathy, the main barrier having been the large amount of data in high resolution retinal photographs. Since the field of telescreening in diabetic retinopathy is new, the advantages and limits of this new modality have not been fully investigated. However, a significant number of research activities related to this field of development have been initiated during recent years. The communication of patient data, notably fundus photographs, over long distances require a common and unambiguous language. In the context of telescreening for diabetic retinopathy this means standardization of terms, clinically as well as technically. The challenges encountered in this standardization are related to data acquisition, data transmission, and data analysis.

Data acquisition

Data needed:

Presently, there is no general agreement on which clinical data is necessary for the screening for diabetic retinopathy, but there is a gradual convergence towards some general principles. Thus, most centers agree that screening for diabetic retinopathy should include non-stereoscopic fundus photography of the central parts of the retina corresponding to the seven fields defined in the ETDRS Research Group standard (1991), and the measurement of best corrected visual acuity using a visual acuity chart complying with the standards used in the ETDRS Research Group standard study. There is also general agreement that diabetes type, diabetes onset, and diabetes duration should be integrated into the decision making when interpreting results. Some centers also routinely do stereo fundus photography and use blood pressure and metabolic control for the interpretation of the eye data.

Image acquisition

In clinical practice a large number of fundus camera types are used for documenting diabetic retinopathy, the main difference being the angular width of the fundus background which is covered, and consequently how many images are necessary in order to cover the relevant parts of the retina.

Previously, fundus images were recorded on photographic film that was the only storage medium with high enough resolution to discern all relevant details. The resolution of digitized fundus cameras has increased steadily during recent years and the technical development has now reached a stage where the minimally required digitial resolution of at least 2048 * 2048 pixels/inch can be achieved.

In a screening setting where fundus images are recorded far from where the assessment of the image content is done, it is important to make a primary assessment of the images to ensure that the quality is good enough for assessing retinopathy. Thus, technical imperfections such as wrong working distance, too small pupils, or bad alignment of the eye in relation to the fundus camera may cause imperfections that can be corrected by repeating photography while the patient is there, instead of being noticed at the distantly located assessment site. One of the major challenges in future will be to develop image processing routines that can act as prefilters to flag out images with bad image quality.

Data transmission

The first studies initiated within medical image transmission were performed using closed lines connecting larger institutional units. With the world-wide extension of the internet, this communication medium is presently the only realistic medium that allows a fast and inexpensive access of larger hospital institutions, private ophthalmologists, other screeners, and patients to interchange image data (Fossen 1998). The EU-funded project OPHTEL was initiated with the aim of developing telemedicine services within ophthalmology, especially diabetic retinopathy (www-ophtel.gsf.de). The project partners from Germany, Italy, England, and Denmark have successfully studied both clinical, logistic and technical parameters of relevance for transmitting fundus photographs obtained in a screening setting for diabetic retinopathy (Mann et al. 1998; Williamson & Keating 1998; Liesenfeld et al. 1999; Piehlmeier et al. 1999). The software has presently been adapted to a setting named "Dansk Teleoftalmologi" based at the Department of Ophthalmology, Århus University Hospital, Denmark, offering free telemedicine services to all Danish ophthalmologists (www.teleoftalmologi.dk). The main concern has been to ensure a maximum level of data security. Although total protection from misuse is impossible, proper encryption of transmitted data and password protection has resulted in a security level that is similar to that used for financial transactions on the internet, and this security level is actually much higher than that of the regular mail service.

Data analysis

The assessment of clinical data consists of two parts. The first part is the extraction of information about retinopathy in fundus photographs into grading scales useful for evaluating the severity of the disease. This should improve the presently practiced routines where retinopathy is graded semiquantitatively by comparison with a set of standard photographs. The other part calls for an appropriate response if one or more of the individual clinical parameters are beyond a certain threshold level. This should lead to simple answers to questions such as:

A) Is the examination normal or not?
B) When should the patient be called for the next screening examination?
C) Should the patient be referred to an ophthalmologist for further evaluation or treatment?

The future challenges within assessment of clinical data involve computer evaluation of pathological lesions in fundus photographs in order to obtain a full quantitative analysis of the retinopathy grade and the integration of relevant clinical parameters into decision models (Gardner et al. 1996; Bek 1998; Sinthanayothin et al. 1999; Ege et al. 1999; Sivieri et al. 1995).

Conclusion

Information technology has a considerable potential in diabetic eye screening.

Telescreening for diabetic retinopathy may allow access to standardized, updated, and quality assured screening services, by diabetic patients in their local environment. Standards for semiquantitative clinical assessment of diabetic retinopathy from fundus photographs are already available, but this data should be integrated with other clinical background parameters into decision models that can be used to draw the optimal consequences of the clinical examination. Technical standards are now available for recording digital images and transmitting them for central assessment via the internet. However, there is a need for the development of computerized algorithms for sensitive, specific and reproducible extraction of data about pathological lesions in retinal photographs with diabetic retinopathy lesions. We anticipate that within a few years a technical basis will be established that can ensure the full exploitation of information technology in telescreening for diabetic retinopathy.

Socio-economic Aspects

About 700,000 patients are estimated to have proliferative diabetic retinopathy in the United States, of whom 130,000 have high-risk characteristics. 500,000 have macular edema, which may be clinically significant in 325,000 (Aiello et al. 1998). High-risk proliferative diabetic retinopathy and clinically significant macular edema have an estimated incidence of 29,000 and 56,000 new cases per year, respectively. As a result, 5,000 Americans/year develop legal blindness secondary to

diabetic retinopathy (Aiello et al. 1998). A crude incidence of 1.8 new blind/100,000 population each year in the United States is comparable to that of other countries in the industrialized world, as the latest figures published in Western Europe show new blindness due to diabetic retinopathy at 1.55/100,000 population/year in 1987–91 in Northern Italy (Porta et al. 1995) and 1.6/100,000 population/year in 1990–93 in Germany (Wurttemberg-Hohenzollern) (Trautner et al. 1997). In spite of efforts to curb it, there are reports of increasing incidence of diabetes-related blindness in Europe, with 2.01/100,000 in 1994 in Wurttemberg-Hohenzollern (Krumpaszky et al. 1999) and in Italy (Porta, unpublished data).

All this has huge human and financial costs. As much as $624 million in social security expenditure, and 173,540 person-years of sight, could be saved every year in the United States if all people with type 1 and 2 diabetes received appropriate eye care (Aiello et al. 1998), without even considering indirect costs and the patients' reduced quality of life.

The reason for the continuous high rate of blindness is that the quality of health care remains unsatisfactory. Although 60% of people with diabetes were estimated to receive appropriate eye care in the US in 1987, 55% of patients with high-risk proliferative diabetic retinopathy and clinically significant macular edema had never had laser photocoagulation (Klein et al. 1991). In 1984, 11% of type 1 and 7% of type 2 patients with high-risk proliferative diabetic retinopathy had not been seen by an ophthalmologist in the previous 2 years (Witkin & Klein 1984). In Britain, in 1995, 47% of cases of proliferative diabetic retinopathy diagnosed at the first outpatient eye visit had been detected previously by screening but 29% had presented because of the onset of symptoms, while 65% of maculopathies are found at screening and only 12% of cases present symptomatically (Bailey et al. 1998). Poor education and lower socio-economic status are additional risk factors associated with proliferative diabetic retinopathy and visual loss in the US (Klein et al. 1994) and Europe (Chaturvedi et al. 1996).

Since diabetic retinopathy can at best be delayed but not prevented by medical treatment, and since the best chances of preserving vision are obtained when photocoagulation is applied to high-risk diabetic retinopathy before it has caused symptoms, structured screening for sight-threatening lesions remains the only option to prevent diabetes-related blindness. There are few reports on the favourable outcome of screening programmes but none, for understandable ethical reasons, are controlled. Iceland, where a national screening programme was started in 1980, is a good case in question (Kristinsson et al. 1994), as are the reports from Sweden: both Lund (Agardh et al. 1993) and Stockholm County (Backlund et al. 1997). Major determinants of success remain the sensitivity of the screeners, i.e. their ability to detect true positives, and the efficiency of the referral chain. It has been estimated that 260 new cases of blindness could be prevented every year in England and Wales if the sensitivity were 87% (Rohan et al. 1989). However, the relationship between screening sensitivity and overall results is not a linear one. According to Javitt's simulation based on US data, the savings in person-years of sight and to the federal budget rise sharply as the screening sensitivity moves from 0 to 40%, but then plateaues as the latter reaches 50–60% and above (Javitt et al. 1995).

From a cost-effectiveness point of view, screening for high-risk diabetic retinopathy makes sound financial sense. The costs per diabetic patient screened, found to have sight-threatening diabetic retinopathy and treated as a result, vary in the health systems of different countries. Early calculations done in the West of Scotland in 1979–82, suggested that each patient treated as a result of screening cost UK £378, compared with 3,575 pounds per year presumably saved in social benefits for the blind (Foulds et al. 1983). In the US, in 1989, the cost per person-year of vision saved from proliferative diabetic retinopathy was $966 and that per person-year saved from macular edema was $1,118 compared with the cost of $6,900/year, at the time, of social security expenditures (Javitt et al. 1989). In Italy, in 1996, the costs per patient screened were about 25 Euros and those per patient treated as a result of screening about 550 Euros, against a yearly social expenditure ranging between 10,000 and 15,000 Euros per blind patient (Porta et al. 1999). It has been estimated that the assumed current 60% level of implementation of eye care in the US saves $348,9 million to the Federal budget and 101,360 person-years of sight. Each additional patient who enters a screening and treatment program, beyond this level, would produce net lifetime savings of $9,571 if he/she has type 1 diabetes, $1,715 in the case of insulin treated type 2 diabetes, and $725 in the case of non-insulin treated diabetes (Javitt et al. 1994). In particular, 71.3% of blindness prevented among type 2 patients would result from macular edema (Javitt et al. 1994). As mentioned above, if 100% eye care could be delivered, the overall figures for America would rise to $624 million and 173,540 person-years of sight saved, respectively (Aiello et al. 1998).

Table 2. Cost per quality adjusted life year (QALY) for some medical procedures.

Program	Cost US$/QALY
Screening for diabetic retinopathy	3,190
Coronary artery bypass (left main coronary)	5,100
Neonatal TSH screening	7,650
Intensive insulin Rx (DCCT)	19,987
School tuberculin testing	53,000
Hospital haemodialysis	65,500
Liver transplant	250,000

Preventing blindness is also effective from the quality of life point of view. Indeed, screening for, and treating, diabetic retinopathy was shown to be the most cost-effective medical procedure known today, with $3,190 per QALY (Quality-Adjusted Life Years) (Table 2). This compares favourably with $7,650 per QALY gained in the screening of neonatal hypothyroidism, or $5,100 per QALY obtained from coronary by-pass surgery (Javitt & Aiello 1996). It is worth remembering here that intensive insulin treatment entails $19,987 per QALY gained at 1996 costs (all others are 1986-adjusted) (Diabetes Control and Complications Trial Research Group 1996). Since health economists suggest that any medical procedure involving costs of less than 20,000 US $ per QALY gained is definitely worth implementing (Laupacis et al. 1992), it makes one wonder how health authorities set their priorities, considering how little attention is paid to preventing diabetes-related blindness and, in contrast, how widespread are, for instance, haemodialysis at 65,000 US $ per QALY or liver transplants at 250,000 US $ per QALY (Javitt & Aiello 1996).

Conclusion

Screening and preventive treatment is essential in the prevention of blindness from diabetic eye disease. Screening can be carried out directly by the ophthalmologist or indirectly through a photographic screening technique. Technological advances and telescreening are under development and may be implemented in the near future. The public benefit of a public health approach in diabetic eye disease with screening and preventive treatment is beyond question. Populations which enjoy this approach generally have a low and decreasing incidence and prevalence of blindness, whereas diabetic blindness remains common and even increasing in diabetic populations not involved in screening programs.

From a socioeconomic point of view screening programs are very cost effective. Comparing to the cost of the prevention programs, the cost to society is 7–20 times greater by ignoring prevention and taking the consequences and supporting the blind. To this can be added the personal tragedies of unnecessary blindness. Most major medical organisations and the World Health Organisation through the St. Vincent program recommend screening for diabetic eye disease. In Sweden, the National Board of Health and Welfare has included regular screening for retinopathy for all diabetic patients in the national guidelines for diabetes. This policy should be adopted by all nations.

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Optic Nerve Oxygen Tension in Pigs and the Effect of Carbonic Anhydrase Inhibitors

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Purpose. To evaluate how the oxygen tension of the optic nerve ($ONPo_2$) is affected by the administration of the carbonic anhydrase inhibitors dorzolamide and acetazolamide and by alterations in oxygen and carbon dioxide in the breathing mixture.

Methods. Polarographic oxygen electrodes were placed in the vitreous humor immediately over the optic disc in 20 anesthetized pigs. Blood gasses and cardiovascular physiology were monitored. $ONPo_2$ was recorded continuously with breathing gasses of 21% O_2-79% N_2, 100% O_2, 20% O_2-80% N_2, and 5.19% CO_2-19.9% O_2-74.9% N_2. Acetazolamide (15–1000 mg) and dorzolamide (6–1000 mg) were administered intravenously.

Results. The mean (± SD) $ONPo_2$ was found to be 24.1 ± 11.6 mm Hg when the pigs were breathing room air and 50.7 ± 29.3 mm Hg when they were breathing 100% O_2 ($n = 15$; $P < 0.001$). In response to breathing 5.19% CO_2, $ONPo_2$ changed from 20.8 ± 5.6 mm Hg (with 20.0% O_2) to 28.9 ± 3.6 mm Hg ($n = 4$; $P < 0.001$). Intravenous injections of 500 mg dorzolamide increased $ONPo_2$ from 16.4 ± 6.1 mm Hg to 26.9 ± 12.2 mm Hg; or 52.5% ± 21.2% ($n = 5$; $P = 0.017$). A dose-dependent effect on $ONPo_2$ was seen with intravenous dorzolamide doses of 1000, 500, 250, 125, 63, 27, 15, and 6 mg. Intravenous injections of 500 mg acetazolamide increased $ONPo_2$ from 23.6 ± 9.5 mm Hg to 30.9 ± 10.0 mm Hg ($n = 6$; $P < 0.001$), and a dose-dependent effect was seen with doses of 1000, 500, 250, 125, 31, and 15 mg.

Conclusions. $ONPo_2$ is significantly increased by the carbonic anhydrase inhibition of dorzolamide and acetazolamide, and the effect is dose dependent. These data demonstrate for the first time a direct effect of carbonic anhydrase inhibitors on $ONPo_2$. (*Invest Ophthalmol Vis Sci.* 1999;40:2756–2761)

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Studies of optic nerve oxygen tension ($ONPo_2$) go back to Ernest in 1973,[1] and several investigators have reported on $ONPo_2$ in a number of species.[2–4] Novack et al.[5] studied the oxidative metabolism of cytochromes in the optic nerve in the cat and found it to be sensitive to arterial blood pressure, intraocular pressure, and oxygen. Cranstoun et al.[6] reported intra- and extravascular oxygen tension measurements in the pig optic nerve.

In the brain, systemically administered acetazolamide leads to increased cerebral blood flow.[7] Rassam et al.[8] found

that intravenous acetazolamide increased retinal blood flow, whereas Grunwald and Zinn[9] found no effect of oral acetazolamide on macular blood flow evaluated with the blue-field entoptic technique. Harris et al.[10] reported that the application of one drop of 2% dorzolamide decreased arteriovenous transit time and increased the velocity of fluorescent particles in the paramacular and peripapillary microcirculations, whereas no effect was seen on flow velocity in the retrobulbar vessels. In contrast, Grunwald et al.[11] found no significant change in the hemodynamic parameters of the retinal circulation after application of topical dorzolamide. Although the results of blood flow studies are not all in agreement, perhaps because of differences in method, they suggest that blood flow, and consequently oxygen delivery, may be affected in the optic nerve region in association with carbonic anhydrase inhibition.[7-11]

The purpose of this study was to develop an experimental preparation suitable for studying $ONPo_2$ and to examine how it is affected by drugs such as carbonic anhydrase inhibitors and physiologic conditions such as inspiration of oxygen and carbon dioxide.

Materials and Methods

Danish agricultural pigs (Landrace), 25 to 33 kg in weight and brought up in a specific pathogen-free environment, were used. Their treatment was supervised by a veterinarian and followed the decrees of the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. All experiments were conducted during daytime.

Animal Preparation

The pigs were anesthetized with midazolam and ketamine, followed by intravenous application of 250 mg mebumal, with additional dosages as needed throughout the experiment, and 0.5 mg/h fentanylum, and atropine as needed. The pigs were paralyzed using 16 mg an hour pancuron bromide. They were intubated and automatically ventilated (model MCM-801; Dameca, Copenhagen, Denmark). The respiratory frequency and stroke volume were kept constant during the experiments. The right pupil was dilated with 1% tropicamide eye drops and 2.5% phenylephrine eye drops. An arterial catheter was placed in a femoral artery for continuous measurement of blood pressure and intermittent blood gas analysis. A venous catheter was placed in a femoral vein for continuous infusion of the anesthetics and saline as needed and the injection of the study drugs. A rectal thermoprobe provided a continuous reading of body temperature.

The pig was secured with surgical tape laterally on an operating table, and a speculum was placed between the right eyelids. A conjunctival peritomy was performed and 3-0 silk sutures placed under the rectus muscle tendons to immobilize the eye. A sclerotomy was made 2.5 mm behind the limbus in the superonasal quadrant and a cannula placed, through which the polarographic electrode was advanced into the vitreous cavity.

Oxygen Measurements

The electrode was held in a micromanipulator (Stoelting, Chicago, IL) and placed in the vitreous humor approximately 0.5 mm (one half the width of the electrode probe) over the optic disc in an area not covered by the large vessels. The entire operation was performed using an operating microscope (Carl Zeiss; Oberkochen, Germany), and the electrode was placed using an indirect ophthalmoscope or the microscope and a flat corneal contact lens. The location of the electrode was checked repeatedly using the indirect ophthalmoscope during the experiment. The placement of the electrodes was found to be stable, and readjustment was rarely necessary.

A silver-silver chloride reference electrode was placed in the conjunctival sac of the same (right) eye and kept moist with saline. The polarographic oxygen meter consists of a 100-μm platinum-iridium electrode inside a 20-gauge needle (model 761; Diamond Electrotech, Ann Arbor, MI), a silver-silver chloride reference electrode, and a chemical microsensor (model 1251; Diamond Electrotech). The recording system was calibrated before and after each experiment in a calibration cell (Diamond Electrotech) at 37°C in 0.9% saline using 100% N_2, 5.0% O_2-95% N_2, and 20% O_2-80% N_2 (provided by AGA, Copenhagen, Denmark).[12] The barometric pressure was monitored, and the oxygen tension recordings were adjusted for barometric pressure and expressed as mm Hg.

The experiments were all run with typical indoor illumination (white fluorescent light tubes (TLM 40W/29RS; Philips, Eindthoven, The Netherlands). The ambient light intensity at the level of the pig's eye was measured with a digital light meter (Mavolux; Gossen, Ehrlangen, Germany) and found to be 497 lux or 6 W/m^2.

Arterial blood samples were obtained at regular intervals, and arterial partial oxygen pressure (Po_2), pH, and arterial partial carbon dioxide pressure (Pco_2) were measured with a blood gas analyzer (model 605 Radiometer, ABL, Copenhagen, Denmark) (Table 1). Arterial blood pressure, electrocardiogram, and rectal temperature were monitored continuously, and it was verified that these values were within normal limits. The output of the Po_2 amplifier, together with continuous recordings of arterial blood pressure and the electrocardiogram, was digitized on-line with an analog-to-digital converter (MacLaboratory 4/e; ADInstruments, Melbourne, Australia). The digitized recordings were fed into a computer (Power Macintosh; Apple; Cupertino, CA). Data were displayed and analyzed with the software provided (Chart ver. 3.5.4/s; ADInstruments) and printed (LaserWriter II; Apple).

Table 1. Physiological Parameters in Experimental Pigs

Parameter	Level
Heart rate (per minute)	113.6 ± 33.2 (65–187)
Blood pressure (mmHg)	100.9 ± 16.2 (75–127)
pH	7.61 ± 0.042 (7.49–7.66)
Pco_2 (kPa)	4.04 ± 0.471 (3.3–5.55)
Po_2 in air (kPa)	13.67 ± 1.46 (10.57–17.43)
Po_2 in 100% O_2 (kPa)	70.13 ± 4.85 (61.54–76.45)
Rectal temperature (C)	38.28 ± 1.09 (36.7–40.7)
Electrode drift (% O_2/h)	0.033 ± 0.061 (0.006–0.214)

Data are expressed as mean ± SD (range).

Experimental Protocol

Each experiment was begun with the animal breathing 100% O_2. Once a stable $ONPo_2$ level was obtained, the breathing mixture was changed to air containing 21% O_2-79% N_2, and a

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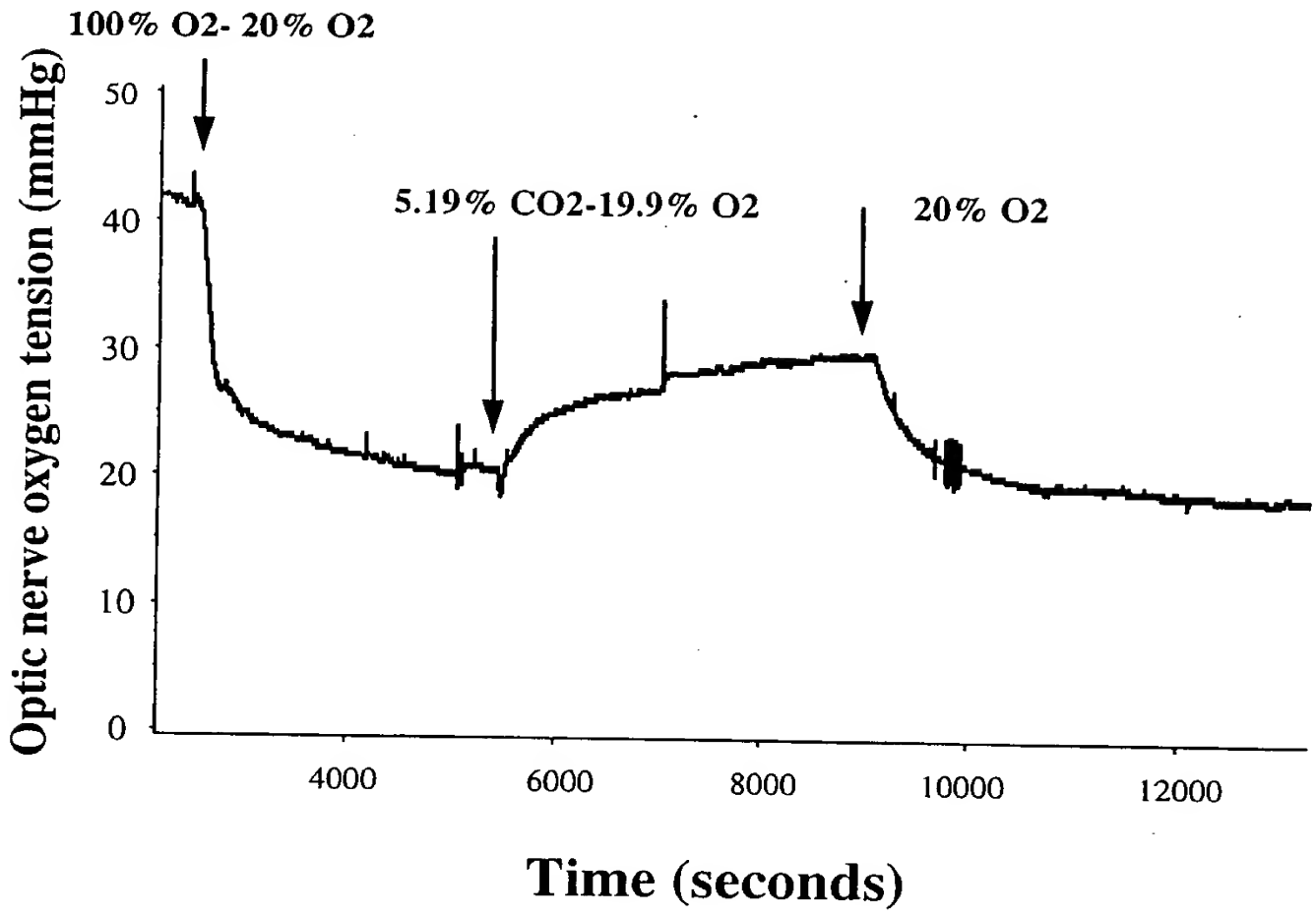

FIGURE 1. Continuous $ONPo_2$ recording during changes in breathing mixture. Time from beginning of record is shown (in seconds) on the horizontal axis and oxygen tension (in millimeters of mercury) on the vertical axis. At the point indicated by the *arrow* on the *left*, the breathing mixture was changed from 100% O_2 to 20% O_2. The *middle arrow* indicates when the breathing mixture was switched to 5.19% CO_2-19.9% O_2. The *arrow* on the *right* indicates when the breathing mixture was returned to 20% oxygen (N_2 to balance). Note the increase in $ONPo_2$ during exposure to CO_2.

stable level was obtained again. In four experiments the breathing mixture was changed to 20% O_2 followed by 5.19% CO_2-19.9% O_2-74.9% N_2, followed by 20% O_2-80% N_2.

The test drug, dorzolamide (MSD, Glostrup, Denmark) (4%, 6–500-mg doses) or acetazolamide (Diamox, Wyeth Lederle Nordiska, Solna, Sweden) (15–500 mg) were injected intravenously into the femoral venous catheter. Dorzolamide was dissolved in 0.1 M sodium citrate buffer (pH 5.6). Acetazolamide was dissolved in saline. In some cases repeated injections of 500 mg dorzolamide and acetazolamide were performed to evaluate the effect of 1000 mg of each drug and whether the effect could be saturated. Intravenous control injections of 20 ml physiological saline and sodium citrate buffer were performed while $ONPo_2$ was monitored.

In three experiments the intraocular pressure was fixed at 20 cm saline (15 mm Hg) with a needle in the anterior chamber connected to a saline reservoir, and recorded with a pressure transducer, whereas dorzolamide was injected intravenously and $ONPo_2$ recorded. Means and SDs were calculated and differences evaluated with a paired Student's *t*-test.

RESULTS

The Effect of Inhaled O_2 and CO_2

Stable recordings of $ONPo_2$ could be obtained reliably for up to 8 hours. The mean $ONPo_2$ was 24.1 ± 11.6 mm Hg when the pigs were breathing air and 50.7 ± 29.3 mm Hg when they were breathing 100% O_2 ($n = 15$; $P < 0.001$). Figure 1 shows an experiment in which the animal first inhaled 100% O_2. When the oxygen content was reduced to 20% O_2, there was an immediate reduction in $ONPo_2$.

In response to breathing 5.19% CO_2-19.9% O_2 (N_2 to balance), $ONPo_2$ changed from 20.8 ± 5.6 mm Hg to 28.9 ± 3.6 mm Hg ($n = 4$; $P < 0.001$). An example of this increase in $ONPo_2$ is illustrated in Figure 1, which also shows that almost immediately after returning to 20% O_2-80% N_2, $ONPo_2$ returned to its value before CO_2 was administered. As shown in Table 2, breathing CO_2 significantly lowered arterial pH and also increased arterial Pco_2, but had no significant effect on arterial Po_2.

TABLE 2. Effect of Breathing Carbon Dioxide and of Study Drugs on Arterial Blood Gas Pressures and pH

	Arterial pH		Arterial PO2 (kPa)		Arterial PCO2 (kPa)	
	Before	After	Before	After	Before	After
CO2 ($n = 4$)	7.62 ± 0.05	7.42 ± 0.03*	13.84 ± 1.1	14.13 ± 0.93	3.96 ± 0.46	6.82 ± 0.52*
Acetazolamide, 500 mg ($n = 6$)	7.62 ± 0.01	7.49 ± 0.03*	14.79 ± 1.67	13.62 ± 1.5	3.84 ± 0.33	5.29 ± 0.57*
Dorzolamide, 500 mg ($n = 5$)	7.57 ± 0.01	7.43 ± 0.05*	12.96 ± 1.58	12.36 ± 0.7	4.42 ± 0.72	6.02 ± 0.87*

Data are expressed as means ± SD, before and after introduction of carbon dioxide and study drugs.
* $P < 0.001$.

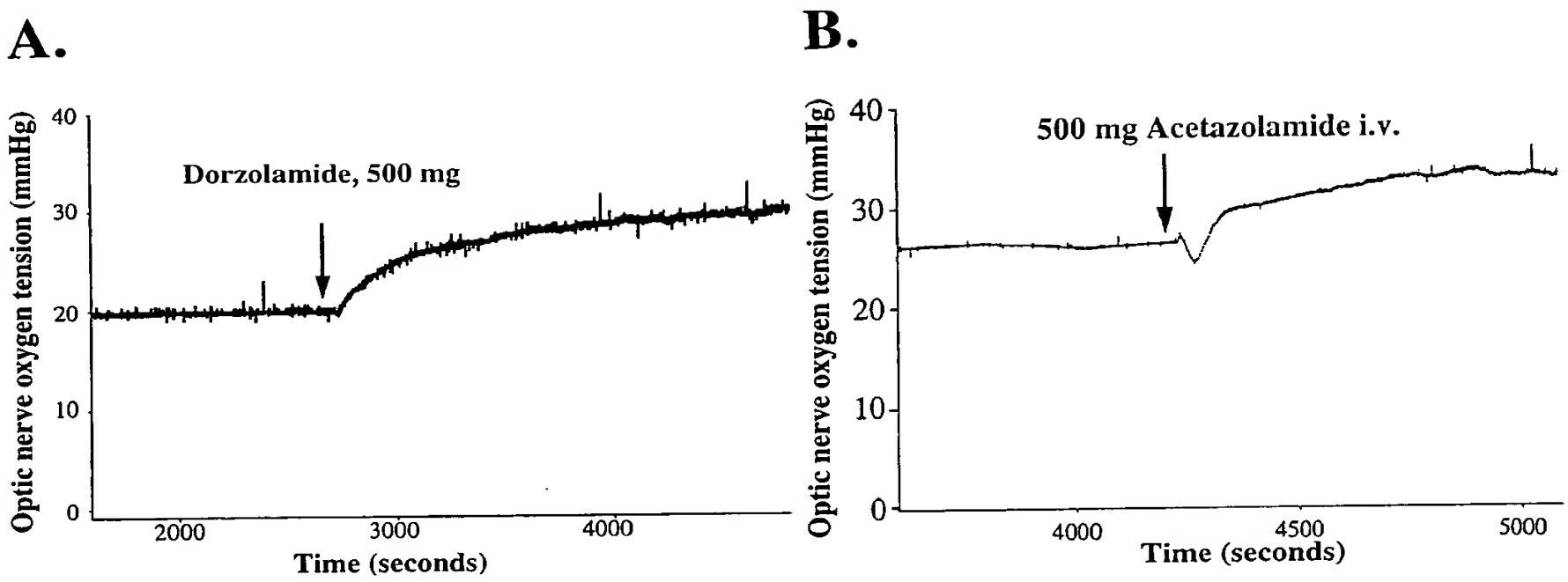

FIGURE 2. (A) The effect of intravenous dorzolamide on $ONPo_2$. Time from beginning of record is shown (in seconds) on the horizontal axis and oxygen tension (in millimeters of mercury) on the vertical axis. At the point indicated by the *arrow*, an intravenous 500-mg injection of dorzolamide was administered. (B) The effect of intravenous acetazolamide on $ONPo_2$. At the point indicated by the *arrow*, an intravenous injection of 500 mg acetazolamide was administered. A transient lowering of arterial blood pressure followed the injection and resulted in the transient dip in $ONPo_2$.

The Effects of Carbonic Anhydrase Inhibition

Intravenous injections of 500 mg dorzolamide increased $ONPo_2$ from 16.4 ± 6.1 mm Hg to 26.9 ± 12.2 mm Hg, or 52.5% ± 21.2% ($n = 5$; $P = 0.017$; Fig. 2A). As shown in Table 2, dorzolamide significantly lowered arterial pH, and also increased arterial Pco_2, but had no significant effect on arterial Po_2. The effect of dorzolamide on $ONPo_2$ was dependent on the dose injected and was seen with dosages of 1000, 500, 250, 125, 63, 27, 15, and 6 mg (Fig. 3). Most of the effect of dorzolamide was reached at 500 to 1000 mg total dosage, and additional injections of the drug had only a small effect on $ONPo_2$. Control intravenous injections of 20 ml of the vehicle sodium citrate buffer solution alone had no effect on $ONPo_2$ in three experiments.

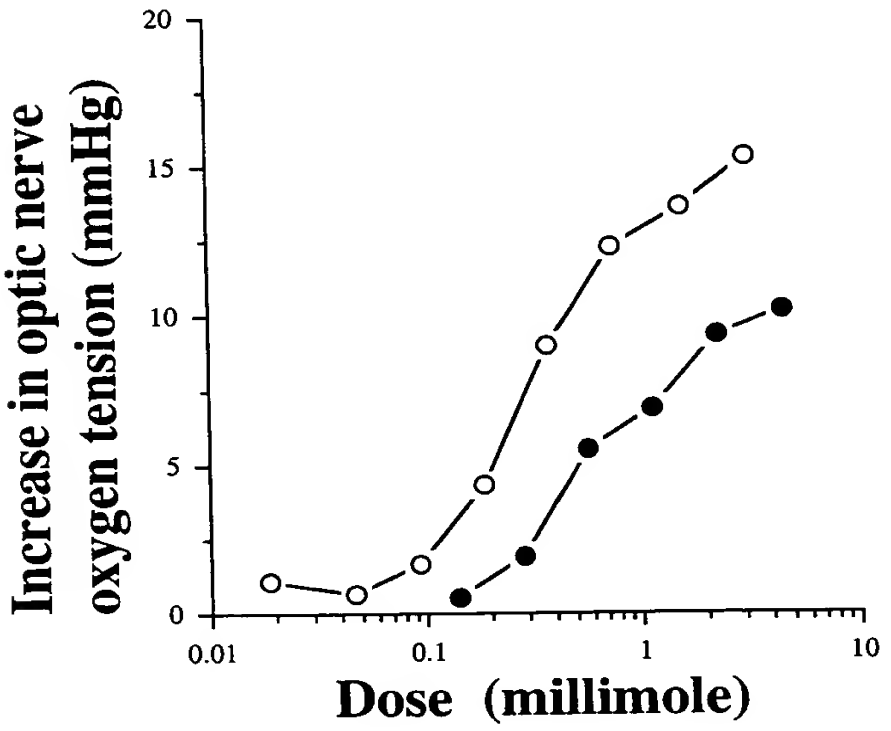

FIGURE 3. Dose-response relationship between intravenous acetazolamide (●) and dorzolamide (○), expressed in log millimoles, and increase in $ONPo_2$ (expressed as change in millimeters of mercury).

Intravenous injections of 500 mg acetazolamide increased $ONPo_2$ from 23.6 ± 9.5 mm Hg to 30.9 ± 10.0 mm Hg ($n = 6$; $P = 0.0008$). Figure 2B shows a typical response to intravenous injection of acetazolamide. This effect on $ONPo_2$ was also seen after injections of 250, 125, 31, and 15 mg acetazolamide and with 1000-mg dosages administered in two equal doses (Fig. 3). Control intravenous injections of 20 ml saline had no effect on $ONPo_2$. As indicated in Table 2, 500 mg acetazolamide significantly lowered arterial pH and also increased arterial Pco_2, but had no significant effect on arterial Po_2. Additional injections of 500 and 1000 mg acetazolamide had little further effect on $ONPo_2$ after initial administration of 1000 mg acetazolamide, indicating that a maximum effect had been reached by the injections first administered. The effects of acetazolamide and dorzolamide on $ONPo_2$ were dose dependent, and dorzolamide was more potent, as illustrated in Figure 3. The effect of dorzolamide injections on $ONPo_2$ was also present when the intraocular pressure was fixed at 15 mm Hg.

DISCUSSION

The discovery that the carbonic anhydrase inhibitors dorzolamide and acetazolamide markedly and significantly elevated $ONPo_2$ offers for the first time clear evidence that these drugs have a direct effect on $ONPo_2$.

The effects of dorzolamide and acetazolamide on $ONPo_2$ were dose dependent. The effect was seen over a dosage range from 1000 mg down to 6 mg for dorzolamide and 1000 to 15 mg for acetazolamide. Lower doses were not tested. The effects were saturated by injection of 500 to 1000 mg of either drug, probably because these dosages fully inhibited carbonic

anhydrase. However, breathing carbon dioxide further increased $ONPo_2$ after a saturation dose of carbonic anhydrase inhibitor had been applied.

In Figure 3 the dose-response pattern is shown as the relationship between the dose of drug in millimoles in each pig and $ONPo_2$ response. Molecule for molecule, dorzolamide has roughly three times the effect of acetazolamide. Sugrue et al.[13] found dorzolamide to be approximately twice as effective as acetazolamide in inhibiting carbonic anhydrase isoenzyme IV and almost 19 times as effective in inhibiting isoenzyme II, whereas acetazolamide is more effective in inhibiting isoenzyme I. This suggests that carbonic anhydrase isoenzyme IV may be involved in this process.

Our data clearly demonstrate the dose dependency of the oxygen tension effect; we recorded an effect at 6 mg dorzolamide. Maren et al.[14] found an effective daily dose of 2% dorzolamide in both eyes three times a day to be 4 mg, because the red blood cells accumulate the drug over a period of days. Sugrue[15] reported that topically applied dorzolamide reaches the retina in pigmented rabbits and that the retinal concentration is approximately 5 μg/g. In contrast, Conroy[16] suggested that topically applied sulfonamides penetrate poorly into the back of the eye and may reach the retina and optic nerve through blood circulation.

The effect of dorzolamide on $ONPo_2$ is independent of the intraocular pressure-lowering effect of the drug. Even when the intraocular pressure is clamped at 15 mm Hg, the oxygen tension effect is still present. Elevated intraocular pressure can lower $ONPo_2$ in the pig.[17] Carbonic anhydrase inhibitors such as dorzolamide may increase $ONPo_2$ through a dual mechanism: lowering of intraocular pressure and a direct effect on $ONPo_2$.

The vasculature of the pig optic nerve head has features that are in common with the human, as well as features that are different.[18] The blood supply of the optic nerve head in the pig eye, as in the human eye, is distinct from that of the surrounding fundus. In the pig there is a continuous arterial circle of Zinn-Haller around the optic disc. The laminar regions of the disc are supplied by vessels arising from the circle of Zinn-Haller, as well as branches of the posterior ciliary arteries. As in humans, vessels in the prelaminar region of the optic disc are derived from the choroid, and laminar branches from the Zinn-Haller circle contribute to the blood supply. In the pig, the capillaries in the surface layer of the disc arise from smaller vessels at the disc margin originating from the prelaminar retinal vessels or from the circle of Zinn-Haller, rather than from recurrent branches from circumpapillary vessels, as in humans. The capillary nets supplying the nerve head are clearly trilaminar, and peripapillary zone 1 has four layers, whereas the human angioarchitecture is far less distinctly laminar.[18]

The change in $ONPo_2$ may be related to a change in optic nerve blood flow and may be the result of blood flow change. Acetazolamide and dorzolamide increase $ONPo_2$, and previous studies have shown that the carbonic anhydrase inhibitors increase cerebral and retinal blood flow.[7,8,10] Our technique cannot reliably distinguish between the effects from the different vascular beds that involve the optic disc head. The cells in the optic nerve region are affected by their chemical environment and the concentration of oxygen and nutrients, which naturally reflects the regional blood flow and metabolism. Oxygen tension is a more direct measure of the cellular environment than is evaluation of blood flow.

In the experiments in which the breathing mixture alternated between 21% and 100% O_2, $ONPo_2$ showed a robust and near immediate response. Placing the tip of a polarographic Po_2 electrode 0.5 mm above the optic nerve head is clearly sensitive enough to measure changes in $ONPo_2$ in response to various physiologic conditions. Our results showing that 100% O_2 breathing elevated $ONPo_2$ is in agreement with Ahmed et al.[2] and Pournaras et al.,[3] who also found that systemic hyperoxia increased periarteriolar but not intervascular oxygen tension.

$ONPo_2$ increased markedly when pigs breathed carbon dioxide. Breathing carbon dioxide and the carbonic anhydrase inhibitors lowered arterial blood pH and elevated blood Pco_2 (Table 2). It is tempting to speculate that the oxygen tension effects of the carbonic anhydrase inhibitors may be linked through the influence of pH and Pco_2.

Acetazolamide and dorzolamide are commonly used in the treatment of glaucoma, and our data suggest that these drugs may affect the glaucomatous optic nerve through two distinct mechanisms. One is the traditional intraocular pressure-lowering effect, and the other is the direct effect on $ONPo_2$. Further research is needed to find whether this effect is seen with other glaucoma drugs and to explore the importance of optic nerve oxygen metabolism in the pathophysiology of glaucoma and its treatment.

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